Contribution of the 24 hour electrocardiogram to the prediction of sudden coronary death

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Abstract

***Background*—Sudden coronary death is a major public health issue. The identification of patients at high risk should therefore be as efficient as possible. This study compares simple and more elaborate risk stratification procedures.**

***Methods*—Risk functions for the prediction of sudden death were determined in a population of 6693 consecutive patients who had 24 hour electrocardiography for various indications. The functions were based on the clinical and electrocardiographical data on 245 patients who died suddenly during 2 year follow up and 467 patients randomly drawn from the total study population.**

***Results*—The model based on history (age, sex, myocardial infarction, congestive heart failure, palpitation, syncope, use of diuretics, and use of nitrates), 12 lead electrocardiography (major intraventricular conduction defect, T wave abnormality, and ST depression $\geqslant 0{\cdot}05$ mV), and standard rhythm analysis of 24 hour electrocardiography (ventricular tachycardia, frequent premature atrial complexes, sinus tachycardia (>150 min^{-1}), and atrial fibrillation) was almost as efficient in the prediction of sudden death as extended models that also contained information from exercise testing, echocardiography, ventriculography, and computer-aided re-analysis of 24 hour electrocardiography (QT and RR interval variability).**

***Conclusions*—These results indicate that additional information from advanced function tests does little to increase the efficiency of prediction of sudden coronary death over that of tests based on history, the standard 12 lead electrocardiogram, and 24 hour electrocardiography.**

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Sudden coronary death is a major public health issue. There are more than 300 000 such deaths every year in the United States.[1] One of the main problems in the prevention of sudden coronary death is the identification of patients at high risk. Many single risk factors for sudden coronary death have been identified,[2] however, little is known about the increase in the efficiency of the prediction of sudden death when information from more advanced tests is added to that derived from simple clinical characteristics.

In this paper we describe risk functions for the prediction of sudden death in patients who had 24 hour electrocardiography for various clinical conditions. We have evaluated their efficiency in identifying those patients most likely to die suddenly within two years of 24 hour electrocardiography. Risk functions were developed in a stepwise manner in the order in which clinical information becomes available. The first risk function was based only on the disease history. Subsequent risk functions included standard 12 lead electrocardiography, blood tests, data from standard rhythm analysis of 24 hour electrocardiograms, an exercise test, echocardiography, computer-aided analysis of 24 hour electrocardiograms, and contrast ventriculography.

Patients and methods

STUDY COHORT

We studied all 6693 consecutive patients who had 24 hour electrocardiography in one of the four participating hospitals between 1 August 1980 and 31 December 1984. Indications for 24 hour electrocardiography were the evaluation of symptoms potentially related to cardiac arrhythmias (palpitation, dizziness, syncope, angina) (65%), of the effect of antiarrhythmic therapy (8%), of risk after myocardial infarction (10%), or a search for a cardiac cause of transient ischaemic attacks or strokes (7%).

FOLLOW UP

Patients were followed for mortality in the two years after 24 hour ambulatory electrocardiography. Follow up was complete in 99·5% of the patients: 716 patients had died (10·7%). The cause and circumstances of death were determined from the records of general practitioners and hospitals. Patients were considered to have died suddenly if death was observed and had occurred within one hour after new or more serious symptoms and if it was likely that the cause was cardiovascular. Also, patients who unexpectedly died during sleep or died while unobserved were considered to have died suddenly if circumstantial evidence pointed to sudden death from cardiovascular causes. All cases of sudden death were independently verified by two senior cardiologists. A total of 245 cases of sudden death was identified.

COLLECTION OF BASELINE DATA

Baseline characteristics were retrospectively collected for all patients who died suddenly and a random sample of 467 patients from

the complete study cohort (including 21 cases of sudden death). A sample twice that of the sudden death group was chosen because of efficiency considerations.[3] Information was collected from the medical records on the following patient characteristics at the time of 24 hour electrocardiography: known cardiovascular risk indicators, cardiovascular history, cardiovascular function tests if available, routine laboratory studies, current drug use, data on standard 12 lead electrocardiograms, data on standard rhythm analysis of the 24 hour electrocardiograms, and indices derived from computer-aided analysis of the original 24 hour electrocardiograms (Appendix A). Evidence of cardiac dysfunction was considered to be present if there had been a history of symptoms of pump failure or an ejection fraction <40% at cineangiographic or radionuclide ventriculography. Details on analyses of the data from the standard 12 lead electrocardiograms and the computer-aided analysis have been reported elsewhere.[3-5]

RISK FUNCTION DEVELOPMENT AND ASSESSMENT

The object of the analysis was to find the combination of baseline variables that most accurately predicted the occurrence of sudden death within two years of 24 hour electrocardiography. The most efficient and rational method of evaluating the risk of sudden death is a quantitative synthesis of the major risk factors for sudden death into a composite score. This was accomplished by the use of a logistic regression function (Appendix B).

Variables selected from univariate analysis (for details see Algra *et al*[3]) were sequentially entered into the model until no remaining candidate variable had a significance level of 0·10. For this purpose the SAS procedure LOGIST was used.[6] For consecutive models we presented groups of variables for inclusion. For each model we calculated risk estimates for each patient to check whether the predicted risk accorded with the observed

Table 1 Sudden death in relation to presence or absence of selected baseline characteristics at the time of 24 hour electrocardiography

Characteristic	2 year sudden death rate: Present (%(n))	2 year sudden death rate: Absent (%(n))	RR*	95% CI
Demographic characteristics:				
Male	4·9 (186/3812)	2·1 (58/2795)	2·4	1·7 to 3·4
Age ⩾60	5·4 (178/3325)	2·0 (66/3282)	2·7	2·0 to 4·0
History:				
Angina	6·3 (140/2207)	2·4 (104/4400)	2·7	2·0 to 3·9
Myocardial infarction	7·2 (151/2092)	2·1 (93/4515)	3·5	2·6 to 5·0
Congestive heart failure	9·7 (101/1046)	2·6 (143/5561)	3·8	2·8 to 5·9
Palpitation	2·5 (82/3311)	4·9 (162/3296)	0·5	0·4 to 0·7
Syncope	5·0 (58/1161)	3·4 (186/5446)	1·5	1·0 to 2·2
Stroke	5·8 (41/702)	3·4 (203/5905)	1·7	1·1 to 2·7
Intermittent claudication	6·2 (30/487)	3·5 (214/6120)	1·8	1·1 to 3·3
Diabetes mellitus	7·5 (40/530)	3·4 (204/6077)	2·2	1·4 to 3·8
Current use:				
Cigarettes	3·6 (83/2279)	3·7 (161/4328)	1·0	0·7 to 1·4
Alcohol >6 units/day	7·0 (18/258)	3·6 (226/6349)	2·0	1·0 to 3·7
Digitalis	7·8 (121/1548)	2·4 (123/5059)	3·2	2·4 to 4·7
β Blockers	4·3 (70/1634)	3·5 (174/4973)	1·2	0·9 to 1·8
Nitrates	6·8 (106/1548)	2·7 (138/5059)	2·5	2·0 to 4·0
Diuretics	9·3 (143/1534)	2·0 (101/5073)	4·7	3·4 to 6·8
Antihypertensive drugs	8·0 (47/588)	3·3 (197/6019)	2·4	1·6 to 4·1
Standard 12 lead electrocardiography:				
Major Q waves (1·2 + 1·3)†	8·5 (74/874)	2·5 (110/4414)	3·4	2·4 to 5·5
Major ST depression (4·1 + 4·2)	7·5 (78/1046)	2·7 (122/4472)	2·7	2·1 to 4·5
Negative or flat T wave (5)	5·8 (154/2666)	2·3 (87/3741)	2·5	1·9 to 3·7
Major ventricular conduction defect‡	11·1 (43/387)	3·2 (186/5747)	3·4	2·2 to 6·3
CIIS 10–30§	5·2 (112/2150)	1·3 (42/3210)	4·0	2·8 to 6·4
CIIS ⩾30	8·3 (87/1046)	1·3 (42/3210)	6·4	4·4 to 11·0
QTc leads I, II, III (ms)	5·3 (65/1233)	2·5 (111/4357)	2·1	1·4 to 3·1
24 hour electrocardiography, standard rhythm analysis:				
PVC ± doublets	3·1 (153/4859)	1·0 (12/1161)	3·0	1·7 to 5·9
Ventricular tachycardia‖	11·9 (80/674)	1·0 (12/1161)	11·5	6·5 to 27·3
Ventricular bigeminy	6·8 (86/1261)	2·9 (159/5432)	2·3	1·8 to 3·7
Frequent PAC (<30%)	8·5 (40/473)	3·3 (205/6220)	2·6	1·7 to 4·7
Supraventricular tachycardia	5·3 (92/1734)	3·1 (153/4959)	1·7	1·3 to 2·5
Atrial fibrillation	7·4 (32/430)	3·4 (213/6263)	2·2	1·3 to 3·7
Sinus arrhythmia	2·1 (52/2508)	4·6 (193/4185)	0·4	0·3 to 0·6
Sinus bradycardia (<50 min^{-1})	2·4 (42/1748)	4·1 (203/4945)	0·6	0·4 to 0·9
Sinus tachycardia (>150 min^{-1})	0·6 (4/645)	4·0 (241/6048)	0·2	0·1 to 0·4
24 hour electrocardiography, computer-aided analysis:				
Maximum heart rate <100 min^{-1}	5·6 (59/1056)	2·9 (134/4594)	1·9	1·2 to 3·1
Minimum heart rate ⩾65 min^{-1}	6·2 (69/1105)	2·7 (124/4545)	2·3	1·5 to 3·8
Short-term RR variation <25 ms	7·0 (86/1228)	2·3 (99/4250)	3·0	2·1 to 5·0
Mean QTc <400 or ⩾440 ms	3·1 (65/2064)	1·3 (36/2678)	2·3	1·5 to 4·0
Maximum QTc <440 or ⩾480 ms	3·4 (64/1892)	1·3 (40/3046)	2·6	1·6 to 4·3
Cardiac function tests:				
LV dilatation at echocardiography	8·7 (109/1247)	2·5 (135/5360)	3·5	2·6 to 5·3
Maximum load exercise test <70%	10·1 (45/444)	3·2 (199/6163)	3·1	1·9 to 5·1
Ejection fraction <40%	22·3 (48/215)	3·1 (196/6392)	7·3	4·0 to 13·8

RR, relative risk; CI, confidence interval; AV, atrioventricular; CIIS; Cardiac Infarction Injury Score; PVC, premature ventricular complex; PAC, premature atrial complex.
*Calculated from the ratio of sudden death rates in which the rate in the patients without the characteristic was taken as the reference standard; †numbers in parentheses are Minnesota codes; ‡left bundle branch block (7·1) or intraventricular block (7·4) or right bundle branch block and left anterior fascicular block (7·8); §see Rautaharju *et al*[11], CIIS <10 was taken as reference; ‖absence of PVC, or ventricular doublets, or tachycardia was taken as the reference standard.

Table 2 Indicator variates retained in the logistic regression models for the prediction of sudden death on the basis of history, 12 lead electrocardiography, standard rhythm and computer-aided analysis of 24 hour electrocardiography, exercise test, echocardiography, and ventriculography

	M1 (n = 684)		*M2 (n = 667)*		*M3 (n = 480)*	
Indicator	*Coefficient*	*SE*	*Coefficient*	*SE*	*Coefficient*	*SE*
History:						
Age ⩾ 60 years	0·75	0·21	0·35	0·22	0·63	0·27
Male	0·78	0·22	0·86	0·23	0·77	0·27
Myocardial infarction	0·74	0·20	0·63	0·22	0·45	0·27
Congestive heart failure	0·70	0·23	0·49	0·24	—	—
Palpitation	−0·47	0·20	−0·59	0·21	−0·62	0·25
Syncope	0·65	0·23	0·70	0·25	0·82	0·30
Stroke	0·48	0·27	—	—	—	—
Alcohol use >6 units/day	0·69	0·41	—	—	—	—
Current drug use:						
Diuretics	1·03	0·21	0·78	0·22	0·76	0·26
Nitrates	0·50	0·21	0·48	0·22	—	—
Antihypertensive drugs	0·49	0·28	—	—	—	—
12 lead electrocardiography:						
Major IVCD*			1·22	0·36	0·91	0·42
Flat or negative T wave†			0·47	0·27	0·69	0·28
ST depression ⩾0·05 m V‡			0·51	0·26	—	—
24 hour electrocardiography, standard rhythm analysis:						
Ventricular tachycardia			0·87	0·26	0·96	0·32
Frequent PAC (>30%)			1·23	0·32	1·13	0·38
Sinus tachycardia (>150 min^{-1})			−1·03	0·62	—	—
Atrial fibrillation			0·61	0·34	—	—
24 hour electrocardiography, computer-aided analysis:						
Maximum heart rate <100 min^{-1}					0·70	0·28
Maximum QTc <440 or ⩾480 ms					0·52	0·25
Exercise test:						
Max load < 70% norm or not available					1·12	0·28
Echocardiography:						
Dilatation of left ventricle (EDD ⩾55 mm)					1·14	0·28
Ventriculography:						
Ejection fraction < 40%					1·05	0·46
Constant§	−5·49		−5·72		−7·02	

M1, history only; M2, M1 + 12 lead electrocardiography + standard rhythm analysis of 24 hour electrocardiography; M3 all data available; M, model; IVCD, intraventricular conduction defect; —, variable did not meet significance level for entry; EDD, end diastolic diameter.
*Left bundle branch block or intraventricular block or right bundle branch block with left anterior fascicular block (Minnesota codes 7.1, 7.4, and 7.8); †Minnesota code 5; ‡Minnesota code 4.1 or 4.2; §corrected to enable the calculation of absolute risks, see appendix B.

risk. For this purpose patients were grouped into five subgroups according to estimated risk: low, medium low, medium, medium high, and high risk. Each subgroup contained about the same number of cases. For each subgroup the mean of the individual risk estimates was compared with the observed risk.[7] We used receiver-operator characteristic (ROC) curves to compare the information content of the models.[8] The more a ROC curve is located in the upper left corner of the graph the higher the information content of the risk function is—that is, the higher both the sensitivity and specificity for the prediction of sudden death.

Results

UNIVARIATE ANALYSIS

Table 1 shows the occurrence of sudden death in relation to selected baseline characteristics at the time of 24 hour electrocardiography. Age ⩾60 years, male sex, history of angina, myocardial infarction, congestive heart failure, and a ventricular aneurysm clearly increased the risk for sudden death with relative risk estimates ranging from 2·4 to 4·5. Patients complaining of palpitation had half the risk of sudden death as those without. Patients with a history of stroke, intermittent claudication, or diabetes mellitus had an approximately twofold risk for sudden death. Patients using digitalis, nitrates, diuretics, or antihypertensive drugs also had a clearly higher risk. Indices of poor left ventricular function as expressed by left ventricular dilatation at echocardiography (end diastolic diameter ⩾55 mm[9]), a low maximum work load at bicycle exercise testing, or an ejection fraction <40% had clear risk implications.

Virtually all classification items of the Minnesota code[10] except code 2, were related to sudden death. Patients with a normal Cardiac Infarction Injury Score (CIIS[11])—that is, <10—had a low risk for sudden death (1·3%), while patients with scores between 10 and 30 had a fourfold and those with a score >30 had a sixfold risk. The lower part of the table shows the occurrence of sudden death in relation to the indices derived from standard rhythm analysis of the 24 hour electrocardiograms. Patients without premature ventricular complexes, ventricular doublets, or ventricular tachycardia were at low risk for sudden death (1·0%). Those with premature ventricular complexes or ventricular doublets had a three times higher risk and those with ventricular tachycardia had a more than tenfold increase in risk. Patients with frequent premature atrial complexes—that is, occurring during 30%—90% of the recording time—and those with atrial fibrillation had twice the risk for sudden death as those without these supraventricular arrhythmias. Patients with sinus arrhythmia, sinus bradycardia (<50 min^{-1}), or sinus tachycardia (>150 min^{-1}, detected in episodes in which heart rate gradually increased and decreased and P waves could be detected) had *lower* risks. The relation of sudden death to selected RR and QTc interval indices derived

Table 3 Risk of sudden death within two years of 24 hour electrocardiography predicted by logistic models 1–3 and observed risk

	M1 (n = 684)		M2 (n = 667)		M3 (n = 480)	
Risk score	*Pred*	*Obs*	*Pred*	*Obs*	*Pred*	*Obs*
Low risk	1·1	1·2	1·0	1·2	1·2	1·0
Medium low risk	3·8	3·4	4·7	3·6	5·2	5·1
Medium risk	7·6	7·3	9·2	10·5	10·6	10·9
Medium high risk	13·7	12·5	15·6	19·7	19·1	14·0
High risk	26·0	31·1	35·4	28·5	47·9	65·1

Pred, mean of predicted risks for the patients within a risk category; Obs, observed risk for the patients within a risk category.

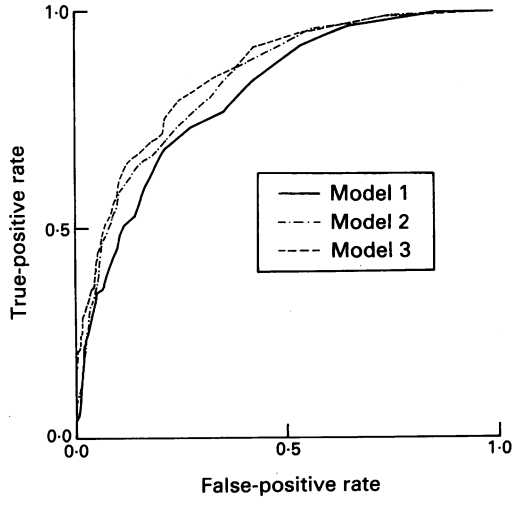
from computer-aided analysis of 24 hour electrocardiograms is shown at the bottom of table 1. A low maximum (<100 min^{-1}) and a high minimum ($\geq$65 min^{-1}) heart rate as well as a lack of short-term heart rate variability (<25 ms) increased the risk of sudden death, as did extremes of mean and maximum QTc duration.

MULTIVARIATE RISK FUNCTIONS

Table 2 summarises three logistic regression models. Model 1 was developed with the use of history only; in model 2 data from standard 12 lead electrocardiography and standard rhythm analysis of 24 hour electrocardiography were added. Common laboratory tests and the cardiothoracic ratio did not reach the significance level required for inclusion when they were added to model 2. Model 2 was extended with data from computer-aided analysis of 24 hour electrocardiography, exercise test, echocardiography, and contrast ventriculography (model 3).

Model 1 was based on 684 patients (21 sudden death patients were selected for the random sample; data for seven patients were incomplete). Model 2 was based on 667 patients because standard 12 lead electrocardiograms were not available in 17 patients. Model 3, including indices derived from the computer-aided analysis of 24 hour electrocardiograms, was based on 480 patients because not all 24 hour electrocardiograms had been subjected to the labour intensive computer-aided analysis (Appendix A). Table 3 shows the predicted and observed risks for sudden death for each of the models 1, 2 and 3. The Figure shows receiver-operator characteristic (ROC) curves based on models 1-3.

Receiver-operator characteristic curves for prediction models 1-3.



Discussion

STEPWISE APPROACH

The risk functions were developed according to a stepwise approach that followed clinical decision making in practice. Disease history is always available to the cardiologist and therefore was used for the basic model 1. Because our study population was defined by 24 hour electrocardiography we judged that data from the standard 12 lead electrocardiogram and standard rhythm analysis of 24 hour electrocardiography should be added next rather than data from bicycle exercise testing and echocardiography. Information from these latter tests and that from contrast ventriculography was entered in the final model (model 3).

PREDICTION MODEL BASED ON HISTORY ONLY

In model 1 age $\geq$60 years and male sex each independently doubled the risk for sudden death within two years after 24 hour electrocardiography. These data correspond well with those from the Framingham study which showed in univariate analysis that males had approximately a 2·5 higher risk for sudden death than females, irrespective of the presence of coronary heart disease.[12] Risk in both sexes increased with age.[12] These relations may be explained by a higher prevalence of atherosclerotic heart disease in men and older people. The known risk factors for cardiovascular disease cigarette smoking, hypertension, hypercholesterolaemia, diabetes mellitus, and family history did not enter the model. The presence of overt heart disease in a large part of the study population probably prevailed over these risk factors. A history of myocardial infarction, stroke, and nitrate use were all included in model 1 and may be interpreted as indicators of advanced atherosclerotic heart disease. Use of diuretics had the strongest independent relation with sudden death in this model (relative risk 2·8). The use of diuretics and the presence of a history of congestive heart failure were both retained in the model; this may be because of the use of diuretics as antihypertensive drugs but may also be attributed to the potassium depleting effects of the thiazide diuretics that can predispose patients to lethal arrhythmias.[13] No conclusions on the relation between drug use and sudden death should be derived from our study because patients with a high risk for sudden death are more likely to have been given such treatment ("confounding by indication").

A history of palpitation was negatively related to sudden death, as reported by Velema.[14] We are not aware of any published pathophysiological explanation for this intriguing finding. A history of syncope must be taken seriously; patients with such a history have about twice the risk of sudden death, which is independent of the other variables taken into account.

PREDICTION MODEL BASED ON HISTORY AND ECG DATA

Model 2 showed a strong independent relation between sudden death and left bundle branch block, right bundle branch block combined with a left anterior fascicular block, and intraventricular block (QRS duration $\geqslant 120$ ms) (relative risk 3·2). These findings accord with those from other studies. These conduction defects are regarded as a manifestation of advanced atherosclerotic heart disease.[15 16] Ventricular tachycardia showed a strong independent relation with sudden death. This relation has often been reported in patients after myocardial infarction[17–22] and also in another study on patients who had 24 hour electrocardiography.[14 23] Ventricular tachycardia indicates a heart at high risk because the myocardium (substrate) is impaired or modulating factors are present.[24 25] Frequent premature atrial complexes were an even stronger independent predictor of sudden death. To the best of our knowledge this finding has never been reported before. A direct relation between premature atrial complexes and the occurrence of sudden death is difficult to explain. Increased diastolic pressure as a result of ischaemic heart disease can cause supraventricular ectopic activity and atrial fibrillation, however. Our data do not support this hypothesis because frequent premature atrial complexes had predictive value independent of indices of left ventricular dysfunction. Patients with sinus tachycardia(>150 min^{-1}) had a lower risk of sudden death than those without. This relation probably shows that patients in good physical condition without overt heart disease are able to do heavy exercise, and do.

EXTENDED PREDICTION MODEL

In the expanded model 3 both a low maximum exercise load and left ventricular dilatation at echocardiography were retained as well as a low ventricular ejection fraction. These three variables, all indicating impaired cardiac function, superseded the importance of a history of congestive heart failure. The fact that all three together entered the model may indicate that they all carry some independent prognostic information. Several variables that just failed to reach statistical significance were dropped from model 2: nitrates, ST depression, sinus tachycardia (>150 min^{-1}), and atrial fibrillation. However, this was largely because model 3 was based on fewer patients than model 2 (480 *v* 667 patients).

INFORMATION CONTENT, RISK FUNCTIONS, AND ASSESSMENT OF FIT

First, risk functions were constructed based on routinely available clinical indices. In the extended model variables from more advanced (and more expensive) tests were added. We used the ROC curves (figure) to evaluate the increasing information content of the models. Model 2 clearly contained more information than model 1, but the extended model (model 3) did not contain much more information than model 2, which was based on history, standard 12 lead electrocardiogram, and standard rhythm analysis of 24 hour electrocardiograms. Thus relatively simple clinical indices predicted sudden death as reliably as models to which information from more advanced tests was added.

The models we developed showed in general a good correspondence between the predicted and observed risk for sudden death (table 3). However, this result may be partly attributable to the fact that the fit was assessed in the same patients as those in which the models were developed.

APPLICABILITY OF THE RISK FUNCTIONS

All patients entered the study because they had 24 hour electrocardiography. So the models can be interpreted only if 24 hour electrocardiography was performed—that is the model based on history only (model 1) is valid in patients in whom 24 hour electrocardiography was indicated but not in those in whom it was not. Because this information is already available it is reasonable to consider model 2 (history, standard 12 lead electrocardiogram, and standard analysis of 24 hour electrocardiogram) as the basic model. We conclude that limited additional information only is gained about the prediction of sudden death if more tests are added to the model. This may have cost-benefit implications for risk stratification after acute myocardial infarction. A high risk for sudden death may be an indicator for treatment, and prevention of sudden death may be attempted in these patients. Furthermore, the risk functions may be used to select high risk patients for intervention studies.

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Table 4 Variables of QTc and RR duration and variability during 24 hour electrocardiography and their definition

Variable	*Definition*
RR interval / heart rate:	
Maximum heart rate	Maximum of per minute heart rate means
Minimum heart rate	Minimum of per minute heart rate means
Short-term variation RR	Mean over 24 hours of per minute standard deviations of RR intervals
QTc interval:	
Mean QTc	Mean over 24 hours of per minute QTc means
Maximum QTc	Maximum of per minute QTc means

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Appendix A

COMPUTER-AIDED ANALYSIS OF THE 24 HOUR ECG

A stream of all RR intervals was obtained during computer-aided analysis of the 24 hour electrocardiograms.[26] Selected indices of RR interval duration and variation are shown in the upper part of table 4. For the calculation of the RR indices only RR intervals between QRS complexes of supraventricular origin were used. Intervals with a duration of <80% or >120% of that of the running RR average were excluded to eliminate intervals related to premature supraventricular complexes and ventricular arrests. Also excluded were the intervals following a short interval (presumably related to a premature supraventricular complex) because these intervals tend to be prolonged as a partially compensatory pause.

QT intervals were measured during automated computer-aided analysis and were reviewed and corrected manually.[27] The lead in which QT interval duration showed the strongest correlation with RR interval duration was selected for QT editing, because the quality of the QT measurements in this lead was considered to be best. Three half hour episodes were selected to limit editing time. From the 48 half hour episodes we selected the episode with maximum short-term RR variability, the episode with maximum QT interval variability (the standard deviation of all QT intervals in a half hour episode), and the episode with the shortest TQ intervals (average of all TQ intervals in a half hour episode). QT intervals not selected for review were adjusted with the mean difference of QT measurements before and after review in the three half hour episodes in that 24 hour electrocardiogram.

All QT data analyses were performed with the use of heart rate corrected QT (QTc) intervals.[28] The definitions of the parameters of QTc interval duration and variation are shown in the lower part of table 4. QTc was calculated only if the current and previous QRS complex were of supraventricular origin. A running RR average with 1/8 update was used in the computation.

Appendix B

LOGISTIC REGRESSION FUNCTION

With the logistic regression function the conditional probability of sudden death given a set of variables x_1, x_2,...,x_j measured at the time of 24 hour electrocardiography is estimated. The function has the form $P = [1 + \exp -(a_0 + b_1x_1 + b_2x_2 + ... + b_jx_j)]^{-1}$ where P is the probability for sudden death when x_1, x_2,...,x_j and a_0, b_1, b_2,...,b_j are coefficients to be estimated from the data. Estimation is by the maximum likelihood method of Walker-Duncan.[29] Constant a_0 needs to be adjusted by a correction a_1 because a_0 is estimated from the data of a *subset* of all 6693 study patients.[30] Correction a_1 is the natural logarithm of $(N_D/N_C)/(n_D/n_C)$ in which N_D is the number of all cases of sudden death, N_C is the number of all non-cases and n_D and n_C are respectively the number cases and non-cases in the model. The absolute risk for an individual patient is obtained by calculation of the sum of the patients coefficients b_1,

$b_2,...,b_j$, the adjusted constant a and transforming it into the absolute risk as follows: $P = 1/[1 + \exp -(a + b_1x_1 + b_2x_2 + ... + b_jx_j)]$.

Besides absolute risk estimates in each model relative risk estimates or odds ratios are obtained directly from the regression coefficients b_1, $b_2...,b_j$. If indicator variables are used, which have a value of 1 if the property considered is present and 0 if it is not, coefficient b_n of variable x_n can be interpreted as the logarithm of the relative risk for sudden death of the presence versus the absence of variable x_n. This relative risk is independent of the other variables retained in the model. It should be noted that this interpretation is conditional upon the data coding strategy.